Annals of Reviews and Research

Juniper Publishers key to the Researchers

Review Article
Volume 8 Issue 1 - October 2022
DOI: 10.19080/ARR.2022.08.555727

Ann Rev Resear

Posterior Reversible Encephalopathy Syndrome: Literature Review and Clinical Challenges

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Submission: October 12, 2022; **Published:** October 21, 2022

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Keywords: Encephalopathy syndrome; Brain autoregulation; Hypoperfusion; Local inflammation

Abbreviations: PRES: Posterior reversible encephalopathy syndrome; MRI: Magnetic resonance imaging; ICU: intensive care unit; RCVS: reversible cerebral vasoconstriction syndrome; EEG: electroencephalogram; ESRD: end-stage renal disease

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neurological condition characterized by abnormal vessel autoregulation and endothelial dysfunction [1]. PRES involves the presence of bilateral reversible vasogenic edema of the subcortical white matter in the parieto-occipital region, which causes a wide variety of acute or subacute neurological symptoms [2,3]. The prevalence of PRES is seen in all age groups with a range from 4 to 90 years and a mean age of 45; women are more likely to suffer from PRES than men. According to the Kid's Inpatient Database in the United States, pediatric patients can also be affected by this condition, accounting for 0.04% of all hospitalizations in 2016, with a mortality rate of 3.2% [2,3]. Risk factors for PRES include arterial hypertension, renal disease, immunosuppressive state, autoimmune disorders, chemotherapy, preeclampsia/eclampsia, infection/sepsis, dialysis, transfusion, surgery, endocrine/metabolic disorders, sickle cell anemia, COVID-19. In most cases, the clinical manifestations of PRES include nonspecific neurological symptoms such as headache, altered mental status, seizures, visual disturbances, nausea, and vomiting [3].

The diagnosis of PRES is usually based on a combination of typical neurological symptoms, radiographic abnormalities, and risk factors. However, it must be noted that the diagnosis cannot be made until other neurological disorders have been ruled out [3]. Magnetic resonance imaging (MRI) of the brain is the standard diagnostic modality, demonstrating focal regions of symmetric hyperintensities on T2-weighted studies, most commonly in the parietal and occipital lobes, followed by the frontal lobes and the cerebellum [2]. Treatment of PRES focuses primarily on addressing the underlying cause, including blood pressure reduction, antiepileptic drugs, sedation, hydration, correcting electrolyte disturbances, and prompt delivery for pregnant women. Although approximately 70% of patients with PRES require intensive care unit (ICU) care, most fully recover within two weeks of onset [3]. This review study aims to provide an overview of the causes, diagnostic approach, and treatment of PRES to facilitate the overall understanding of this complex neurological condition.

Etiology & Pathogenesis

The pathogenesis of PRES is not entirely understood, but it is believed to be associated with dysfunctions in brain autoregulation, hypoperfusion, or local inflammation. It is almost always associated with hypertension, systemic inflammatory processes (such as endothelial injury, sepsis, eclampsia, transplantation, and autoimmune disease), renal failure, general anesthesia, and immunosuppressive medication [4]. In severe uncontrolled hypertension, a disruption in brain autoregulation leads to hyperperfusion and cerebral vessel damage, resulting in interstitial extravasation of proteins and fluids, causing vasogenic edema. Angiography in PRES demonstrates reversible focal and diffuse abnormalities, which are thought to reflect endothelial dysfunction. As blood pressure increases, vasoconstriction may exacerbate pre-existing endothelial dysfunction, leading to hypoxia and subsequent vasogenic edema [5].

According to the mechanism of autoregulation theory, PRES does not often reach the upper limit of autoregulation, nor does it explain why PRES occurs without hypertension, nor does it explain why edema is not directly related to blood pressure severity [5,6]. In addition, although this theory suggests that the brain is hyperperfused, some positron-emission tomography studies have demonstrated the contrary. The alternative hypothesis is that a systemic inflammatory state causes endothelial dysfunction. Nevertheless, this theory does not explain why some PRES cases appear without any evidence of inflammation [6].

Epidemiology

PRES was initially described in the 1996s. Since then, it has been reported in all age groups (4-90 years), predominating in middle-aged adults. Its incidence continues to be highly associated with severe comorbid conditions, such as bone marrow (2.7-25%), solid organ transplantation (0.4%), connective tissue disorders (0.69%), and chronic renal failure (0.84%), with the latter being the strongest predictor of the development of PRES. The incidence of PRES in the ICU pediatric population has been reported to be up to 0.4% [7,8].

Clinical Manifestations

A variety of neurological symptoms characterize PRES. After the condition's onset, clinical manifestations may appear immediately or after several days [9-11]. Patients may present with signs of encephalopathy, including quantitative and qualitative disorders of consciousness such as cognitive deficits, stupor, somnolence, or coma. A deteriorating mental condition may result in respiratory failure, one of the primary reasons for admission to a critical care unit [9,10]. In 74–87% of patients, seizures are seen early in the disease course. Various types of epileptic seizures may occur in these patients, including status epilepticus (3-17%), generalized tonic-clonic (54-64%), and partial seizures (3-28%) [10]. Due to the frequent involvement of the occipital lobes, around 2/3 of all patients with PRES will present with visual abnormalities, including hemianopia, cortical blindness, and visual hallucinations. Fundoscopic examinations are usually normal. However, hypertension has been associated with papilledema, flame-shaped retinal hemorrhages, and exudates [9,10].

Another common symptom is a slow-onset and diffuse headache. Thunderclap headaches in PRES patients should elicit further imaging tests to check for reversible cerebral vasoconstriction syndrome (RCVS). Nausea, vomiting, and consciousness disturbances are less specific neurological symptoms. Focal neurological abnormalities have been recorded in 5–15% of cases, depending on the lesion's location. In 19% of patients, focal neurological impairments such as aphasia and hemiparesis have been noted. In addition, several case studies have recorded myelopathic symptoms in individuals with spinal cord involvement [9,10]. As PRES is often characterized by unclear clinical presentation, the diagnosis has begun to depend more on neuroimaging findings.

Diagnosis

PRES can be challenging to diagnose due to the lack of specificity in the symptoms, vital signs, and laboratory and imaging findings. Furthermore, the diagnosis can only be made after other neurological disorders have been ruled out. Standard criteria for diagnosing PRES include acute onset of neurological disease, neuroimaging abnormalities, and reversible clinical/radiological symptoms. PRES early warning scoring (PEWS) incorporates several clinical parameters, including hypertension, visual symptoms, seizure, consciousness disturbance, and slow electroencephalogram (EEG) waves or epileptic discharges. PRES is diagnosed when 10 or more PEWS points are found [12].

Several laboratory abnormalities can be found in PRES, including elevated levels of LDH in patients with malignancy or preeclampsia and eclampsia, hypoalbuminemia, elevated CRP,

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hypomagnesemia, elevated creatinine, elevated liver enzymes, as well as hyperalbuminemia in the cerebrospinal fluid. Laboratory data needs to be further studied to understand PRES pathophysiology better.

Neuroimaging is essential to diagnose PRES. Brain MRI can reveal vasogenic edema, especially with T2-weighted and fluid-attenuated inversion recovery sequences. Quantification of the apparent diffusion coefficient can be used to differentiate vasogenic edema from cytotoxic edema. The most common finding is a bilateral edematous focal region in the brain hemisphere, affecting parietal and occipital lobes more frequently. Unfortunately, interpretation can vary because these findings often do not correlate with clinical manifestations. EEG can be done to exclude non-convulsive status epilepticus. However, it lacks sensitivity and specificity as no characteristic EEG waves exist for PRES [12,13].

PRES should always be considered among the differentials in patients with risk factors such as end-stage renal disease (ESRD) or hypertension in acute neurological symptoms with typical neuroimaging findings, especially when unexplained by common etiologies [13]. Malignant PRES includes radiological findings consistent with PRES, Glasgow Coma Scale score of less than 8, and clinical decline despite standard elevated intracranial pressure management. The most frequent differential diagnoses are primary or secondary headaches, followed by toxic-metabolic encephalopathy. Eclampsia and preeclampsia associated with PRES are also common. Early and timely neuroimaging makes the diagnosis of PRES easier for physicians. However, neuroimaging misinterpretation can lead to the suspicion of other diseases, such as cerebral infarction, paraneoplastic demyelinating disorder, or acute disseminated encephalomyelitis [12].

Treatment

The management of PRES will depend on the primary cause of the neurologic dysfunction. Treatment strategies include medication to reduce high blood pressure, impaired renal function, or immunosuppressive therapies [14]. Untreated hypertension is considered one of the causes of developing or exacerbating cerebral edema. When preeclampsia occurs, magnesium sulfate is prescribed to prevent seizures, while eclampsia is treated by expediting the delivery of the infant [15]. In the treatment of PRES, corticosteroids have been described. However, using steroids has not been demonstrated to effectively decrease vasogenic edema [16]. A study of 99 PRES patients found that steroids were not significantly associated with the extent of vasogenic edema. PRES complications are treated with IV anticonvulsants in status epilepticus and aggressive management of hemorrhagic PRES and elevated intracranial pressure. It is estimated that approximately 70% of patients with PRES require hospitalization in the intensive care unit [17]. When calcineurin inhibitor-associated PRES occurs, a common and valuable strategy is to replace the offending calcineurin inhibitor with other immunosuppressive agents, usually sirolimus, everolimus, mycophenolate mofetil, or hydrocortisone, as well as other immunosuppressive agents [18]. Treating malignant complications of PRES is also essential and includes IV anticonvulsants (in status epilepticus), aggressive management of hemorrhagic PRES, and increased intracranial pressure [19].

Prognosis

Frequently, the underlying causing condition will determine PRES prognosis. While this neurological condition is generally reversible, it is often associated with subacute to acute neurological complications such as cerebral hemorrhage, cerebellar herniation, and refractory status epilepticus. Some of the factors that have been associated with poor outcomes include severe encephalopathy, hypertensive etiology, neoplastic etiology, hyperglycemia, end-stage renal disease, and atrial fibrillation [20,22]. Complications related to PRES could be diminished with prompt diagnosis using brain imaging because the reversibility of the clinical and radiologic abnormalities is contingent on controlling the cause [21]. MRI imaging severity is correlated with the clinical outcome in most cases. In a recent study, PRES mortality was observed in 19% of the patients, and functional impairments of varying degrees were reported in 44%. Focal neurological deficits like aphasia and hemiparesis were observed in 19% of patients, and residual structural lesions were observed in 40% of cases on follow-up imaging [22]. Long-standing morbidity and mortality can occur in severe forms. In patients with malignant forms of PRES, aggressive care has markedly reduced mortality and improved functional outcomes. Close follow-up (during 90 days posterior to the event) after PRES has become one of the essential factors in obtaining a better recovery due to the need for proper adjustment of pharmacology and control of the disease that causes the syndrome.

Conclusion

Posterior Reversible Encephalopathy Syndrome (PRES) is a complex neurologic condition characterized by a combination of clinical features, predisposing risk factors, and radiologic imaging findings. In PRES, angiography demonstrates reversible focal and diffuse abnormalities, which are thought to be related to endothelial dysfunction. As a result of the multifactorial etiology, lack of specificity in the symptoms, laboratory results, and imaging findings, PRES can be challenging to diagnose. Consequently, the approach to this neurological disorder has begun to rely more on specific neuroimaging findings. Clinical manifestations of this condition include signs of encephalopathy, such as cognitive deficit, somnolence, or coma. Additionally, PRES patients might experience frequent headaches, seizures, visual disturbances, and focal neurologic deficits. In some individuals, the deteriorating cognitive status might result in respiratory failure, which is the main reason for admission to the ICU.

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Treatment of PRES relies primarily on addressing its underlying causes; in most cases, the condition is reversible. However, delayed therapy might result in severe subacute to acute neurological sequelae such as cerebral hemorrhage, cerebellar herniation, and refractory status epilepticus. A combination of aggressive treatment and close monitoring has been found to significantly reduce mortality and improve functional outcomes in patients with malignant forms of PRES. As a result, close follow-up (for 90 days following the event) has become one of the most critical factors to attain a more satisfactory recovery following PRES. During monitoring these patients, it is essential to adjust pharmacologic measures and control the underlying condition causing the neurologic syndrome. In most cases, PRES is associated with a good prognosis. Nevertheless, PRES might become a significant cause of neurological disability when delayed treatment or neurologic symptoms last for long periods. Consequently, future research efforts should focus on developing better and more accurate diagnostic measures in order to provide early treatment and minimize possible complications.

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